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Cost-Effectiveness of the Combined Use of Warfarin and Low-Dose Aspirin versus Warfarin Alone in Egyptian Patients with Aortic Valve Replacements: A Markov Model

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ABSTRACT

Background: The combination of antiplatelet and anticoagulant therapy significantly reduces the rate of thromboembolic events in patients with heart valves compared with anticoagulant therapy alone. Cost-effectiveness of this therapy in Egypt, however, has not yet been established. **Objective:** The aim of the present study was to evaluate the cost-effectiveness of the combined use of warfarin and low-dose aspirin (100 mg) versus warfarin alone in patients with mechanical aortic heart valve prostheses who began therapy at the age of 50 to 60 years over a 5-year period from the perspective of the medical providers. **Methods:** A cohort Markov process model with five health states (recovery, reoperation, bleeding, thromboembolism, and death) based on Egyptian clinical practice was derived from published sources. The clinical parameters were derived from meta-analyses of randomized controlled trials of patients with mechanical valve prostheses. The quality of life of the health states was derived using the available published data. Direct medical costs were obtained from four top-rated governmental cardiology hospitals in Egypt. All costs and effects were discounted at 3.5% annually. All costs were converted using the purchasing power parity rate and are reported in US \$ for the financial year of 2013. **Results:** The total quality-adjusted life-years (QALYs) were estimated to be 1.1616 and 1.1199 for the warfarin plus aspirin group and the warfarin group, respectively, which resulted in

a difference of 0.0416 QALYs. The total costs for the warfarin plus aspirin group and the warfarin group were US \$307.33 and US \$315.25, respectively (the difference was US \$7.92), which yielded an incremental cost-effectiveness ratio of −190.38 for the warfarin plus aspirin group. Thus, the combined therapy was dominant. Various one-way sensitivity analyses indicated that probabilities of reoperation and bleeding in the recovery state had the greatest effects on incremental costs. The model parameters that had the greatest effects on incremental QALYs were the relative risk reduction of death and the utility value in the recovery state. **Conclusions:** The present study is the first cost-utility analysis to conclude that, from the perspective of Egyptian medical providers, combined therapy is more effective and less costly than warfarin alone for patients with mechanical aortic valve prostheses. For clinicians and patients who choose to focus on minimizing thromboembolic risk, these results suggest that combined therapy offers the best protection. This study helps to inform decisions about the allocation of health care system resources and to achieve better health in the Egyptian population.

Keywords: aortic valve replacement, aspirin, cost-effectiveness, Egypt, warfarin.

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Introduction

In developing countries, one of the major causes of valvular heart disease that requires valve replacement is rheumatic fever affecting young adults [1]. In Africa, the combination of a lack of resources, a lack of infrastructure, political, social, and economic instability, poverty, overcrowding, and malnutrition contributes to the persistence of the high burden of rheumatic

valvular heart, which later requires surgery [2]. Although mechanical prostheses have excellent durabilities, they require lifelong anticoagulation therapy to minimize risks of thrombosis and embolism. Warfarin therapy reduces disability and fatal thromboembolic events, but it can also cause disabling and fatal hemorrhagic events. Anticoagulants without antiplatelet agents do not provide adequate protection for patients with mechanical aortic heart valve prostheses [3,4]. The addition of aspirin (80–160 mg

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daily) to warfarin therapy may reduce the risk of thromboembolism and valve thrombosis [5,6].

The initiation of an effective early antithrombotic therapy is important because of its potential effect on the rate of early thromboembolic complications after mechanical aortic heart valve implantation [7,8]. An important question that remains to be answered is whether the combined use of warfarin and low-dose aspirin is more cost-effective than warfarin alone in Egyptian governmental hospitals from the perspective of medical providers. This question is particularly important because a misconception exists in the Egyptian medical community that the added clinical benefit of reducing the risk of complications is not worth the cost. Decision analysis is a quantitative method for synthesizing data from numerous sources for the evaluation of treatment alternatives and was developed to determine the cost-effectiveness of the combined use of warfarin and low-dose aspirin as compared with warfarin only.

Objective

The objective of this study was to evaluate, from the perspective of the medical provider, over a 5-year period, the cost-effectiveness of the combined use of warfarin and 100-mg aspirin compared with that of warfarin alone in patients with mechanical aortic heart valve prostheses who began therapy between the ages of 50 and 60 years.

Methods

A half-cycle corrected Markov cohort process model with the five mutually exclusive health states (recovery, reoperation, bleeding, thromboembolism, and death) was developed (Fig. 1). The structure of this model reflects the natural history of the disease, the current treatment practices, and the published studies in this disease area [9]. This type of decision model is used for analyzing clinical problems involving risks that change or occur repeatedly over time [10]. The five identified health states of the model structure correspond to the real practice of patient management in Egypt and remain as simple as possible. The health states (i.e., model contents) were validated by clinical experts and the data that were available from the authors' institutions. The model was built to reflect patients who began therapy between the ages of 50 and 60 years. Although aortic valve replacement (AVR) can be done at any age, it is most commonly done in patients 45 years and older. A time horizon of 5 years was selected to reflect the long-term consequences of the decisions. To simplify the model, it was adapted to exclude clinical events that were not expected to differ across the compared patients [11] (e.g., perioperative mortality due to primary AVR and prosthetic valve endocarditis);

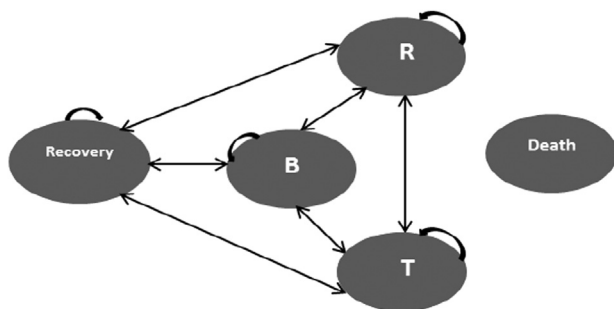


Fig. 1 – Markov state-transition diagram. Not shown are the transitions to the death state. B, bleeding; R, reoperation; T, thromboembolism.

however, the valve-related excess mortality rate described below was included. The combined use of adjusted-dose warfarin and 100-mg oral aspirin (international normalized ratio 2–3) was compared with the use of adjusted-dose warfarin (international normalized ratio 2–3) alone, which is the currently recommended practice. The transition probabilities from the recovery health state to the reoperation, bleeding, thromboembolism, and death states were derived from previously published sources [9,12].

A comprehensive search of PubMed and MEDLINE was conducted for English articles published between 1985 and June 2013 to retrieve the available published data regarding the probabilities of the health states, the relative risks of the combination therapy, and the quality of life in the health states. Randomized controlled trials (RCTs), systematic reviews, and meta-analyses of RCTs were chosen because they provide the least biased and most robust evidence regarding treatment. When RCTs were not available, observational studies were included after considering expert opinions regarding the synthesis of the clinical evidence. Articles that addressed the long-term management of patients with prosthetic heart valves were selected on the basis of terms related to the clinical conditions and the cost-effectiveness of the combination; these terms included the following: “cost-effectiveness,” “aortic valve replacement,” “antithrombotic,” “antiplatelet,” “anti-coagulation,” “aspirin,” “vitamin K antagonist,” “warfarin,” “thrombosis,” “bleeding,” “randomized controlled trial,” “randomized,” “controlled trial,” “meta-analysis,” and “systematic review.” Articles that exclusively included trials that focused on elderly patients were excluded because these trials evaluated a different patient population. Twenty-two relevant articles were identified by this electronic search and were reviewed, and six articles were excluded for the above-mentioned reasons.

The cycle length of the model was 1 month to allow for a precise estimation of the timing of events and related costs because patients are unlikely to experience more than one major event during this time [13]. This study adopted the perspective of a medical provider seeking to maximize the health gains of the population while representing the most efficient use of the finite resources available to Egyptian governmental hospitals [11]. All costs and effects were discounted at 3.5% annually as recommended by Egyptian guidelines [11].

Clinical Parameters

The following five health states were studied: the recovery state, which was defined by the patients being alive without event or recovering after an event; reoperation, which was defined by patients undergoing reoperation or suffering operative morbidity; bleeding, which was defined by the requirement of hospitalization or blood transfusion for a major bleeding event; thromboembolism, which was defined by the patients suffering a thromboembolic event with morbidity; and death, which was defined as death from any cause. All patients who underwent the indexed surgery without morbidity were initially defined as being in the recovery state. Thus, with every cycle, the patients who survived the index surgery could remain in their current health state or could experience the following: bleeding (fatal or non-fatal), valve thrombosis followed by reoperation (fatal or non-fatal), thromboembolism, or death from any cause.

Several assumptions were incorporated to simplify the model. First, the population was assumed to be free of noncardiac life-threatening morbidities. There were neither explicit indications nor contraindications for anticoagulation. Second, we assumed that patients with AVR who experienced major bleeding continued to receive oral anticoagulant therapy because studies have shown that the risks of thromboembolism in patients with mechanical valves who are not on anticoagulant therapy exceed the risks of recurrent bleeding in those receiving anticoagulation

therapy [14]. Finally, we assumed that the patients who underwent reoperation for valve thrombosis had the initial mechanical valve replaced by a new valve.

All model input variables, their ranges, and sources are noted in Table 1. The Egypt-based age-standardized mortality rate was obtained from the World Health Statistics [15]. The excess mortality rate was added to the population-based mortality rate in the model. This excess mortality rate was obtained from a three-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical AVR [12]. The risk for reoperation was obtained from two clinical trials of 211 and 394 patients with AVR who were randomized to receive either tissue or mechanical valves [16,17]. The probability of death with reoperation was obtained from a decision analysis that compared the tissue and mechanical valves in patients with AVR [9]. This probability was calculated using a multivariate logistic regression equation that was adjusted to the age of 50 years from the above-mentioned source [9,18]. The risk of major bleeding, the probability of major bleeding resulting in death, the thromboembolic risk after AVR, the permanent morbidity after thromboembolism or bleeding complications, and the mortality after thromboembolism were derived from a large study (1608 patients) that determined the incidence of complications of oral anticoagulant therapy in patients with mechanical heart valves [19]. We assumed that the transition probabilities from the recovery state to the health states of reoperation, bleeding, and thromboembolism were the same as those for patients in the “reoperation” state.

Relative risk reduction (RRR) and relative risk increase values for the combined use of warfarin and 100-mg aspirin were obtained from published data based on a meta-analysis of randomized trials comparing warfarin plus aspirin and warfarin

alone (hereafter referred to as “warfarin”) in patients with mechanical heart valves (Table 1) [20]. RRR is defined as the difference in event rates between two groups, expressed as a proportion of the event rate in the control group, while relative risk increase is the proportional increase in rates of bad outcomes between experimental and control patients in a trial [21]. RRRs for each end point in the published data were manually calculated by dividing the absolute risk reduction by the pooled event rates for each corresponding control group. It was also assumed that the RRR in the thromboembolism state was identical to that of the patients who experienced valve thrombosis and proceeded to the reoperation state.

Outcomes

The outcomes of the two strategies were measured in terms of quality-adjusted life-years (QALYs). This generic measurement weighs the length of life by the quality of life a patient experiences while in a specific health state. QALYs combine both morbidity and mortality into a single parameter. The quality-of-life measures that were incorporated into the model were derived from a Bayesian Markov model that was developed to compare the cost-effectiveness of patient self-management and physician management of long-term anticoagulation therapy from the perspective of Canadian health care payers [7].

A baseline quality-of-life value for patients without an event or recovery after any event was obtained from a systematic review that was based on clinical outcome data regarding the clinical effectiveness and cost-effectiveness from different studies of the management of long-term oral anticoagulation therapy that compared the self-testing and self-management of oral

Table 1 – Model input variables.

Parameter	Base case	Range		Data source
		Low value	High value	
Probabilities*				
Recovery → Bleeding	0.027	0.013	0.062	[19]
Recovery → Reoperation	0.004	0.002	0.009	[16,17]
Population-based mortality	0.003	0.001	0.004	[15]
Recovery → Death (1st 30 d)	0.071	0.06	0.09	[12]
Recovery → Death (after 1 mo)	0.169	0.13	0.20	[12]
Recovery → Thromboembolism	0.007	0.003	0.013	[19]
Permanent morbidity after thromboembolism	0.67	0.536	0.804	[19]
Thromboembolism → Death	0.044	0.022	0.088	[19]
Permanent morbidity after bleeding complication	0.22	0.176	0.264	[19]
Bleeding → Death	0.122	0.06	0.24	[19]
Reoperation → Death	0.000013	0.000010	0.000015	[9,18]
Utility in recovery state	0.668	0.61	0.76	[22]
Utility in reoperation state	0.45	0.35	0.75	[7]
Utility in bleeding state	0.54	0.44	0.74	[7]
Cost of reoperation event (\$)	7414	4545	11,363	4 top-rated Egyptian cardiology hospitals
Cost of bleeding event (\$)	2116	435	3030	4 top-rated Egyptian cardiology hospitals
Cost of thromboembolism event (\$)	1534	1160	2196	4 top-rated Egyptian cardiology hospitals
Relative risk reduction of thromboembolism (%)	19	12	29	[20]
Relative risk increase of bleeding (%)	3.2	2	5	[20]
Relative risk reduction of mortality (%)	10	6	18	[20]

* Transition probabilities are shown as annual probabilities (which can be converted to 1-mo probabilities with the equation below):

$$tp_1 = 1 - (1 - tp_t)^{1/t}$$

where tp_1 is 1-mo transition probability and tp_t is overall probability over time t .

Table 2 – Reoperation, bleeding, and thromboembolism costs of the 4 top-rated governmental cardiology hospitals.

Four top-rated governmental cardiology hospitals					
Hospital	No. of patients served annually	No. of beds	Cost per bleeding event (\$)	Cost per reoperation event (\$)	Cost per thromboembolism event (\$)
Naser Institute	450,000	850	435	8333	1060
National Heart Institute	365,000	360	2500	5416	1515
Kasr Eleiny Hospital	3,000,000	5152	3030	1136	2196
Ain Shams University Hospital	2,000,000	3200	2500	4545	1363
Mean			2116	7414	1534

anticoagulation treatment to clinic-based monitoring [22]. Because estimates of the patient utilities of reoperation for valve thrombosis are lacking, we assumed that the utility for patients who undergo reoperation was identical to that for patients in the thromboembolism state from the time of the event until death based on data from the above-mentioned sources [7,23]. Because the validity and reliability of these reported QALYs are untested, these estimates were allowed to vary over a wide range in the sensitivity analyses.

Costs

The direct medical care costs of reoperation, bleeding, and thromboembolism events from the perspective of the medical provider were obtained from four top-rated cardiology hospital databases (Table 2) and supplemented with the information that was available from the authors' institutions. This secondary research method provided the best available evidence for the valuation of health service resources in terms of their unit costs. The unit costs were calculated by subtracting the profit margin and sales taxes of each hospital from the hospital charges. No capital costs were included. Cost data for the base case represent the average cost of the four top-rated cardiology governmental hospitals under the public scheme to reflect the actual circumstances in Egypt. A macrocosting approach was used to determine the costs. Given the very low costs of both warfarin and aspirin, the costs of these drugs were not included in the cost analysis. We assumed that there would be no difference in resource use for anticoagulation follow-up across strategies in standard practice (i.e., warfarin was used in both strategies). Thus, costs for the follow-up visits were not included in the model. Local currency conversions to US \$ were performed using the purchasing power parity rate [24]. All costs were reported in US \$ for the financial year of 2013.

Sensitivity Analysis

To test the stability of our results across variations in input model parameter estimates, we performed various one-way sensitivity analyses as recommended by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS): ISPOR Task Force report [25]. The robustness of the model-to-model structures and assumptions was tested with one-way sensitivity analyses of the estimates of clinical parameters, different time horizons, health state utilities, costs of reoperation, bleeding, and thromboembolism, and discount rates for costs and health effects. The ranges of assumptions tested in our sensitivity analyses increased as the data on which we based our assumptions increased in uncertainty. All model inputs were varied through confidence intervals or reasonable ranges that were

determined on the basis of different published sources. All analyses were performed using Microsoft Excel 2010.

Results

The total costs of the two strategies and the corresponding outcomes as experienced QALY values were recorded. The results of the analyses are expressed as incremental cost-effectiveness ratio. The incidences of reoperation over the 5-year time horizon were 0.09% in the warfarin group and 0.08% in the warfarin plus aspirin group. The incidences of bleeding were 0.66% in the warfarin group and 0.69% in the warfarin plus aspirin group. Thromboembolisms occurred less frequently in the warfarin plus aspirin group (warfarin group, 0.21%; warfarin plus aspirin group, 0.16%). Similarly, mortality was lower in the warfarin plus aspirin group (warfarin group, 8.5%; warfarin plus aspirin group, 7.7%).

Across the overall population, the total QALYs of the warfarin plus aspirin group were estimated to be 1.1616 compared with 1.1199 for the warfarin group, which resulted in a difference of 0.0416 QALYs. The total costs for the warfarin plus aspirin group and the warfarin group were US \$307.33 and US \$315.25, respectively (the difference was US \$7.92). These costs yielded an incremental cost-effectiveness ratio of –190.38 for the warfarin plus aspirin group. Thus, the combined therapy strategy was dominant (i.e., more effective and less costly). Table 3 provides the total expected costs and health effects from the base-case analysis.

One-way sensitivity analyses (Figs. 2 and 3) were conducted to identify the model parameters that most strongly affected the incremental QALYs and costs. These analyses indicated that the probabilities of transition to both the reoperation and bleeding states from the recovery state had the greatest effects on incremental costs. The model parameters with the greatest

Table 3 – Decision analytic model results.

Treatment strategy	Model results			
	Total costs (\$)	Total QALYs	ICER	Interpretation
Warfarin + aspirin	307	1.16	–190.38	Dominant strategy
Warfarin	315	1.11		Baseline
Difference	–7.92	0.0416		comparator

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

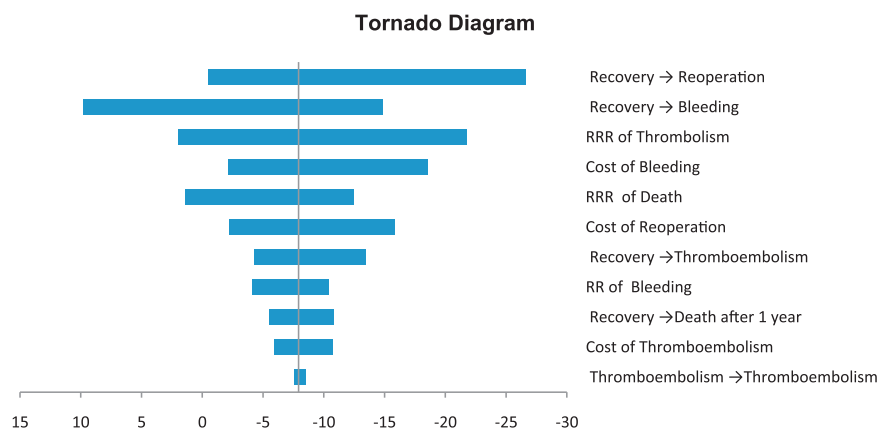


Fig. 2 – Results of the one-way sensitivity analysis of the incremental costs. RR, relative risk; RRR, relative risk reduction.

effects on incremental QALYs were the RRR of death and the utility value in the recovery state.

Given the uncertainty surrounding the point estimates of the relative risks for these outcomes, a sensitivity analysis using confidence interval ranges was conducted as described in published sources [20]. This analysis revealed no effect on treatment decision. Extrapolating the time horizon of the analysis to 10 years resulted in a gain in QALYs and negative incremental costs for the combined therapy, which seemed to be driven by the trend toward decreased mortality in patients who were treated with the combined therapy. The base-case analysis of the present study used the average costs for the four top-rated cardiology governmental hospitals. Sensitivity analysis using the uncertainty ranges estimated from the lowest and highest cost values for the four top-rated cardiology governmental hospitals (Table 1) did not alter the conclusions we have reached. The robustness of the model to changes in quality of life within reasonable ranges determined from published sources was also explored [26]. Sensitivity analysis of the model results did not alter the conclusions reached on the basis of other analyses.

When different commonly used discount rates for both health effects and costs that ranged from 2% to 6% were applied, no major effects on results were found. Treatment decision was not

significantly affected by other values over their clinical ranges (Table 1).

Discussion

The initiation of antiplatelet plus anticoagulant therapy is likely to improve the management of patients with prosthetic heart valves in developed countries, but the most important unmet need and potential for benefit from these therapies is in developing countries in which a massive and rapidly increasing burden of valvular heart disease exists [27]. The results of the model in this study demonstrate that the combined use of warfarin and 100-mg aspirin is more effective and less costly than warfarin alone and should be advocated for patients with mechanical aortic heart valve prostheses. Interestingly, the warfarin plus aspirin group exhibited a small gain in QALYs compared with the warfarin group. Moreover, the costs associated with warfarin plus aspirin were lower than those associated with warfarin alone; therefore, the combined use of warfarin and aspirin is the dominant treatment strategy.

The strength of our model is the use of relative risk data from a meta-analysis of nine RCTs that include trials that were

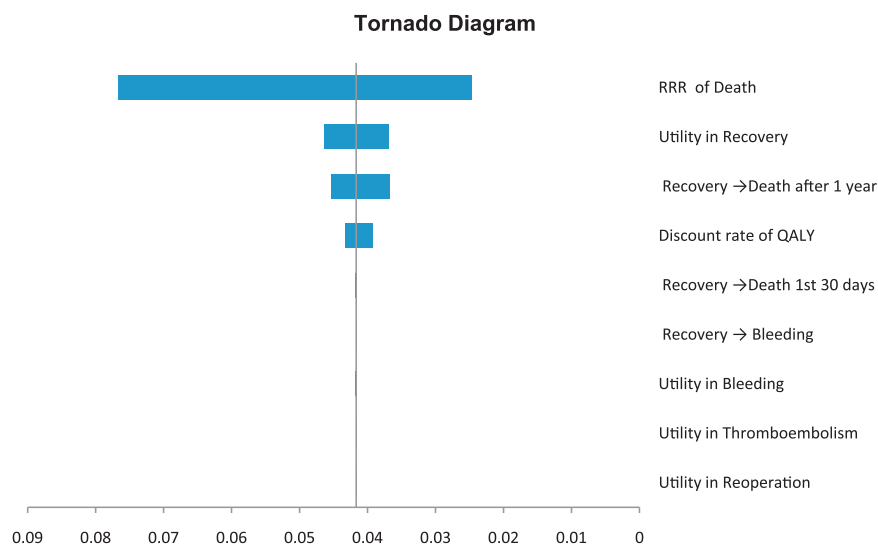


Fig. 3 – Results of the one-way sensitivity analysis of the incremental QALYs. QALY, quality-adjusted life-year; RRR, relative risk reduction.

identified by a systematic, unbiased literature search [20]. In addition, the incorporation of quality-of-life issues may be important for clinical decisions from the perspective of medical providers who seek to improve their patients' lives. The epidemiologic parameters portion of our analysis is supported by publications of RCTs of patients with mechanical valves [16,17]. The present study is the first to incorporate a decision analysis approach that compared the cost of complications and the cost-effectiveness of warfarin plus aspirin versus warfarin alone in patients with mechanical aortic heart valve prostheses because cost-effectiveness analyses of the combined use of warfarin and aspirin are lacking in Egypt and a debate exists between physicians regarding the costs of potential complications.

In our analysis, we explicitly accounted for model input uncertainties by assigning confidence intervals and plausibility ranges based on published sources to the quality-of-life, relative risk, and epidemiologic parameters in the model. This procedure allowed us to perform one-way sensitivity analyses that revealed that these factors did not affect our results. In our base case, the average costs of the four top-rated cardiology hospitals were used. For this reason, the results of our analysis may seem to be limited to patients who are treated in leading cardiology hospitals in which treatment costs are typically higher than those of other hospitals in rural areas. Nevertheless, a sensitivity analysis using lower rates did not lead to a qualitatively different conclusion, which increases the credibility of our analysis. To assess the influences of other model structures and assumptions on the cost-effectiveness estimates, one-way sensitivity analyses of various parameters were performed. These various sensitivity analyses did not result in qualitatively different results, and the model proved to be rather robust. The dominance of the combined therapy versus warfarin only in our model and its robustness in the sensitivity analysis suggest that the combined therapy with warfarin and aspirin should be preferred by the decision makers in Egypt.

The analysis of the present study has several limitations that should be noted. The risk of prosthetic valve endocarditis was not included because of the low rate (<1% at year one) of this complication [28]. Similarly, the incorporation of reoperation and bleeding into one health state is uncommon in contemporary practice and was not incorporated into the baseline model [26]. The rate of thromboembolism on reoperation was assumed to be identical to that for patients in the recovery state because of the absence of reliable data regarding the rate of occurrence of this event. Another potential limitation, quality-of-life values used in the model were transferred from the Canadian population because we have no outcome data available regarding quality-of-life values for the Egyptian population. Certain elements of cost-effectiveness studies are transferable. It was based on four steps that consider data availability and methods for adjusting cost-effectiveness information to a particular jurisdiction [29]. It should also be noted that the incorporation of several simplifying assumptions into the model is a weakness, but this weakness was overcome by the sensitivity analyses that encompassed wide ranges of parameter values.

There are other limitations that need to be considered when assessing the relative generalizability of this study. First, we adopted the perspective of a medical provider and not a societal perspective and thus excluded indirect costs and out-of-pocket direct costs incurred by the patient. Accounting for these costs would likely increase the superiority of the warfarin plus aspirin strategy because increases in QALYs will lead to reduced absenteeism, increased productivity and recovery, and reduced direct nonmedical costs associated with the follow-up. Second, the analysis was primarily based on effectiveness data from a meta-analysis of RCTs that compared the combined use of warfarin and aspirin to warfarin alone in patients aged between

50 and 60 years with mechanical aortic valve prostheses. Thus, the findings cannot easily be generalized to more complex patients including those with risk factors, young adults, and elderly patients. Finally, 16 published articles in English were identified by our electronic search, but we may have omitted some important information that could have been recovered from non-English articles.

The main drivers of the cost-effectiveness of combined therapy in this model was the reduced numbers of thromboembolisms and the reduced mortality rates that occurred among the warfarin plus aspirin groups in the previously performed RCTs. This combined therapy strategy will potentially be applicable to other settings in Egypt because there are no major differences in clinical practices between rural and urban areas; thus, combined therapy will lead to substantial savings in health care system resources.

Conclusions

The present study is the first cost-utility analysis that addresses both the clinical and the economic implications of combined therapy from the perspective of Egyptian medical providers. This study concluded that the combined use of warfarin and aspirin is dominant to the use of warfarin alone for patients with mechanical aortic valve prostheses. Our findings will help inform health care decisions regarding the allocation of health care system resources to improve the health of the Egyptian population. For those clinicians and patients who choose to focus on minimizing thromboembolic risk, these results suggest that the combined therapy offers the best protection and reduced costs because this well-established antithrombotic treatment improves the quality of patient care and reduces the overall costs. Whether this combined therapy is cost-effective in certain subgroups with additional risk factors needs to be addressed in future studies.

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